

PATENT SPECIFICATION

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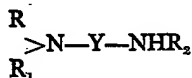
COMPLETE SPECIFICATION

Derivatives of Ethylene Diamine

We, AMERICAN HOME PRODUCTS CORPORATION, a Corporation organised and existing under the laws of the State of Delaware, United States of America, of 22, East 40th Street, New York, 16, New York, United States of America (Assignees of JOSEPH LESTER SZABO and SAMUEL V. LIEBERMAN and WILLIAM F. BRUCE, each a Citizen of the United States of America, of 1028, Drexel Avenue, Drexel Hill, Delaware County Pennsylvania; 724, Hirst Avenue, Havertown, Delaware County, Pennsylvania; and 2949, Normandy Avenue, Ardmore, Delaware County, Pennsylvania, United States of America, respectively), do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to derivatives of ethylene diamine, especially ethylene diamine diformate and its condensation products with aldehydes and ketones.

In our application No. 15582/51 (Serial No. 716,556) we have described and claimed new salts of penicillin and N-substituted diamines having the general formula



wherein R represents an aliphatic, alicyclic, araliphatic, aromatic or heterocyclic group which may or may not have substituents.

R₁ represents a hydrogen atom or an aliphatic, alicyclic, araliphatic, aromatic or heterocyclic group which may or may not have substituents.

R₂ represents a hydrogen atom or, when R₁ is hydrogen, an aliphatic, alicyclic, araliphatic, aromatic or heterocyclic group which may or may not have substituents and

Y represents an alkylene radical having

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from 2 to 12 carbon atoms.

Particularly useful salts are those derived from N-monosubstituted, or N:N-disubstituted, or N:N¹-disubstituted ethylene diamines.

The N-substituted ethylene diamines or salts thereof can be prepared by interacting ethylene diamine with an aldehyde or ketone and formic acid. The process is carried out by reacting the ethylene diamine with the aldehyde or ketone in a medium of formic acid. We have now found that this method can be improved by the use of ethylene diamine diformate, a new salt of ethylene diamine.

According to the present invention therefore a method of preparing N-substituted ethylene diamines is provided which consists in reacting ethylenediamine diformate with an aldehyde or ketone in a solvent and hydrolysing the reaction product.

The use of the diformate makes it unnecessary to use a medium of formic acid. The formic acid medium can be replaced by ethanol, other alcohols or organic solvents or water. Both N-substituted and N:N¹-disubstituted-ethylene diamines result from the reaction, and either one may be selected to be the major product by suitably altering the reaction period and the proportions of reactants: equimolar amounts of aldehydes or ketone and ethylene diamine diformate favour N-substituted ethylene diamines, and doubling the amount of aldehyde or ketone and increasing the reaction period favour N:N¹-disubstituted ethylene diamines.

Substituted ethylene diamine salts may also be prepared by interacting approximately equivalent quantities of a salt of ethylene diamine, such as the dihydrochloride, dihydrobromide, dinitrate or diacetate or other suitable salt of ethylene diamine, and an acid, with formaldehyde either in the form of its aqueous solution or as the solid polymeric form, paraformaldehyde, and with a compound containing an active hydrogen such as

the alpha-hydrogen of thiophenes, picolines, quinaldines, phenols, aliphatic nitro-compounds, organic acids and esters, and open-chain and cyclic aldehydes and ketones in a solvent such as water, alcohol or other organic solvents or mixtures thereof, resulting in an N:N'-disubstituted ethylene diamine salt which may be transposed into the free base by alkali treatment. This method can also be improved by using ethylene diamine diformate as the salt of ethylene diamine.

There is provided, according to one feature of the invention, the new compound ethylene diamine diformate.

This compound has marked utility in the reactions described above. It may be obtained and maintained in anhydrous form much more readily than the free base which may be dried only with difficulty and is extremely hygroscopic. Thus, the diformate is more convenient for use in the first of the above described reactions. Its use in that reaction permits weighing an exact amount without estimating water content, obviates diluting the reaction mixture with water which has a deleterious effect, and obviates the slow, ice-cooled, addition of the free base to strong formic acid in the reaction flask. An additional advantage is that the use of ethylene diamine diformate enables exact equivalents of the reactants to be introduced into solvents other than formic acid.

Ethylene diamine diformate can be prepared simply by mixing ethylene diamine with concentrated formic acid in acetone. In practice, the ethylene diamine should first be diluted with acetone, and added dropwise to a cooled, stirred mixture of concentrated formic acid and acetone.

EXAMPLE 1.

PREPARATION OF ETHYLENEDIAMINE DIFORMATE

120 mls. of crude ethylene diamine diluted with 100 ml. of acetone were added dropwise to a cooled and stirred mixture of 200 ml. 88-90% formic acid and 200 ml. acetone. After complete addition, the precipitated solid was collected on a filter and washed with acetone. The lumpy product was powdered in a mortar to facilitate washing by suspension in acetone. After drying the product weighed 200 grams. A sample recrystallized from methanol formed white crystals, m.p. 132° C. (bar). Anal. $C_4H_{12}N_2O_4$: N, 18.42. Found: N, 18.43.

EXAMPLE 2.

PREPARATION OF N:N'-DIPIPERONYLETHYLENE DIAMINE AND SALTS THEREOF

In a 250 ml. flask fitted with a reflux condenser with drying tube, there were mixed 30 grams (0.2 mol.) of piperonal, 15.2 grams (0.1 mol.) of ethylenediamine diformate, and 50 ml. 98-100% formic acid. The reaction mixture was heated to reflux; after 10 minutes the rate of carbon dioxide evolution was 20

ml. per minute, after 54 hours rate was 0.3 ml. per minute. Most of the excess formic acid was removed under reduced pressure. Then 50 ml. 6N hydrochloric acid were added to the dark residue and the mixture heated on a steam cone for two hours. On cooling, dark crystals formed. These were filtered and washed with isopropanol leaving almost white crystals, m.p. 300° C. (bar). The mother liquors were concentrated to 50 ml. and diluted with 50 ml. water throwing out a dark oil which was removed by benzene extraction. The aqueous phase was diluted with 50 ml. ethanol, heated, treated with charcoal, and on concentration to circa 75 ml. and cooling, an additional crop of crystals were obtained. Recrystallization from aqueous ethanol and from water did not raise the m.p. of the white, crystalline, dihydrochloride above 300° C.

The dinitrate was prepared by adding dilute nitric acid to aqueous dihydrochloride. The white precipitate was re-crystallized from aqueous ethanol m.p. 263° C. (bar).

The dipicrate was prepared by adding aqueous lithium picrate to aqueous dihydrochloride. The yellow precipitate was recrystallized from ethanol. m.p. 213° C. (bar).

EXAMPLE 3.

PREPARATION OF N:N'-BIS-(p-NITROBENZYL)-ETHYLENEDIAMINE AND ITS SALTS

In a 50 ml. flask fitted with a reflux condenser and drying tube, there were placed 3.0 g. (0.02 mol.) of p-nitro-benzaldehyde, 1.5 g. (0.01 mol.) of ethylenediamine diformate and 10 ml. 98-100% formic acid. After heating for 30 hours, 385 ml. (84%) of evolved carbon dioxide were collected. Ten ml. of 6 N hydrochloric acid were added and the mixture was refluxed for 1½ hours. When diluted with 10 ml. water and cooled, light tan crystals separated. The dihydrochloride was collected on a filter, washed with cold water and dried, 2.5 g. (62%). A portion, recrystallized from aqueous ethanol (charcoal), afforded white crystals, m.p. 290° C. (bar). Calcd. for $C_{14}H_{16}N_4O_4Cl_2$: C, 47.66; H, 5.00; N, 13.89; Cl, 17.54. Found: C, 47.73; H, 5.02; N, 13.87; Cl, 17.38.

The dinitrate was prepared by adding dilute nitric acid to aqueous dihydrochloride. The precipitated white crystals were recrystallized from aqueous ethanol, m.p. 220° C. dec.

EXAMPLE 4.

PREPARATION OF N:N'-BIS-(2-THENYL)-ETHYLENEDIAMINE AND A SALT THEREOF

In a 500 ml. three-necked flask, fitted with stirrer, condenser and thermometer, were mixed 42 gms. (0.5 ml.) of thiophene, 38 gms. (0.25 mol.) ethylenediamine diformate and 43 ml. of 36% aqueous formaldehyde (0.5 mol.). The mixture was stirred and heated to gradually raise the temperature. At 60° C. a vigorous reaction began. Heating was stopped and an ice-bath applied to the

5 flask. The internal temperature rose to 73° C. and the reaction mixture solidified. 200 ml. of 50% aqueous alcohol were added and stirred and the mixture was heated an additional 1½ hours. After cooling, the reaction product was filtered and washed with water. The white product was amorphous and did not dry well, nor could it be crystallized.

10 It was dissolved in 250 ml. hot water, cooled, and made alkaline with 40% sodium hydroxide. The free base which separated was not very soluble in ether, and was taken up in benzene, dried over sodium hydroxide and obtained as a colourless, viscous oil on removing benzene *in vacuo*. The oil was converted to diacetate by dissolving in 200 ml. ethyl acetate and adding 12 ml. glacial acetic acid.

The precipitated salt was filtered, washed with ethyl acetate and dried, m.p. 84° C. (bar).

In the manner described in Example 4 20 using 0.25 mol. of the diformate together with half a mol. of formaldehyde, half a mol. of any of the following compounds may be reacted therewith to form the corresponding symmetrical di-substituted alkylene diamines: 25 cyclohexanone, 2-, 3- and 4-methylcyclohexanone, 4-methoxy-cyclohexanone, cyclopentanone, 2-methyl-thiophene, isoquinoline, 3-methyl-isoquinoline and quinaldine.

Using the general procedure already 30 described, the following compounds may be prepared by reacting ethylenediamine diformate with the aldehydes and ketones specified:

MONOSUBSTITUTED DIAMINES.

35	N-undecylethylenediamine	- - - - -	undecylaldehyde
	N-heptylethylenediamine	- - - - -	heptaldehyde
	N-(3:5:5-trimethylhexyl)-ethylenediamine	- - - - -	3:3:5-trimethylhexaldehyde
	N-vanillylethylenediamine	- - - - -	vanillin

DISUBSTITUTED DIAMINES.

40	N:N'-di- <i>n</i> -heptylethylenediamine	- - - - -	<i>n</i> -heptaldehyde
	N:N'-di-undecylethylenediamine	- - - - -	undecylaldehyde
	N:N'-dicyclopentylethylenediamine	- - - - -	cyclopentanone
	N:N'-di-4-methoxycyclohexylethylenediamine	- - - - -	4-methoxycyclohexanone
	N:N'-divanillylethylenediamine	- - - - -	vanillin

45 What we claim is:—

1. As a new compound ethylenediamine diformate.

2. A method of preparing N-substituted ethylene diamines which consists in reacting ethylenediamine diformate with an aldehyde 50 or ketone in a solvent and hydrolysing the reaction product.

3. A method as claimed in claim 2 in which the solvent is an alcohol.

55 4. A method as claimed in claim 2 in which the solvent is formic acid.

5. A method as claimed in any of claims 2 to 4 in which the aldehyde is piperonal.

6. A method as claimed in any of the pre-

ceding claims in which the aldehyde is *p*-nitrobenzaldehyde. 60

7. A method of preparing N-substituted ethylene diamines which consists in reacting ethylenediamine diformate with formaldehyde and a compound containing an active hydrogen 65 atom.

8. The method of making ethylenediamine diformate herein particularly described.

9. The method of preparing N-substituted ethylene diamines from ethylenediamine 70 diformate herein particularly described.

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